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PCT/IB03/03517

सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***860/Del/02*** *dated* ***23rd August 2002.***

Witness my hand this 22nd day of March 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED BUT NOT IN COMPLIANCE WITH RULE 17.1(a) OR (b

0860-02

23 AUG 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF NITROFURANTOIN CONTROLLED RELEASE DOSAGE FORM"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. PUNEET SHARMA
b. PANANCHUKUNNATH MANOJ KUMAR
c. VISHNUBHOTLA NAGAPRASAD
d. SUNILENDU BHUSHAN ROY
e. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, PUNEET SHARMA, PANANCHUKUNNATH MANOJ KUMAR, VISHNUBHOTLA NAGAPRASAD, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Puneetsharma
(PUNEET SHARMA)

b.

(PANANCHUKUNNATH MANOJ KUMAR)

c.

(VISHNUBHOTLA NAGAPRASAD)

d.

(SUNILENDU BHUSHAN ROY)

e. Rajiv Malik
(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **683766** dated **06.08.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **23RD** day of **AUGUST, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

FORM 2

0860-2

23 AUG 2002

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

A PROCESS FOR THE PREPARATION OF NITROFURANTOIN CONTROLLED RELEASE DOSAGE FORM

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention generally relates to a process for the preparation of nitrofurantoin controlled release dosage form, which provides immediate and sustained release of nitrofurantoin.

Nitrofurantoin, chemically known as 1-[(5-nitrofurfurylidene) hydantoin, is a well known antibacterial agent for the treatment of urinary tract infections. Nitrofurantoin is remarkably well-tolerated drug; however, side effects, which occasionally occur with the oral administration of nitrofurantoin, are nausea and emesis. US Patent No. 3,401,221 discloses use of macrocrystalline nitrofurantoin to reduce these side effects.

Further US Pat. No. 4,772,473 discloses a combination sustained release / immediate release pharmaceutical capsule for oral administration of nitrofurantoin for minimizing side effects of nausea and emesis and also for reducing the frequency of dosing from four times daily to twice daily. The immediate release layer described therein comprises macrocrystalline nitrofurantoin whereas sustained release layer comprises nitrofurantoin along with combination of polyvinylpyrrolidone and carboxyvinyl polymer as sustained release polymers.

In the present invention, we have discovered a novel combination of sustained release polymers, which provides excellent sustained release properties to nitrofurantoin and maintains the therapeutic level of nitrofurantoin for more than twelve hours.

The present invention therefore provides a process for the preparation of nitrofurantoin controlled release dosage form comprising

a. a sustained release portion comprising

(i) Nitrofurantoin

(ii) One or more pH dependent hydrophilic polymer(s); and

b. and an immediate release portion comprising macrocrystalline nitrofurantoin

The sustained release portion may optionally contain a pH independent hydrophilic polymer.

Present invention may have one or more pH dependent polymer(s). When one pH dependent polymer is used it is selected such that it produces a viscous gel and provides a near zero order release profile throughout the gastrointestinal tract. However whem more then one pH dependent polymer is employed these are selected in such a way that one provides semi enteric release profile i.e. slow release in stomach and immediate release in the intestine (above pH 6), whereas the other provides slow and linear release throughout the intestinal tract.

The addition of pH independent hydrophilic polymer provides cohesiveness to the mass so that the compact/tablet maintains its structure and integrity as it traverses the gastrointestinal tract.

Such a combination of polymers gels/swells in the gastric fluid to form a viscous matrix, from which only a small amount of nitrofurantoin is released via diffusion. However, in the neutral and alkaline pH of the small intestine, the pH dependent hydrophilic polymer fully hydrates and slowly erodes to release the drug.

The concentration and ratio of the pH dependent hydrophilic polymers is optimized in such a way that the desired release profile is obtained in the intestine. The pH dependent hydrophilic polymer(s) may be used in concentration of 2-20%, whereas pH independent hydrophilic polymer(s) may be used in concentration 0.1-15%.

For the purpose of present invention the word "Nitrofurantoin" includes nitrofurantoin, its pharmaceutically acceptable salts and hydrates.

As used herein "macrocrystalline nitrofurantoin" is particulate crystalline nitrofurantoin as described in United States Pharmacopoeia. The nitrofurantoin as used in the sustained release portion refers to micronized nitrofurantoin monohydrate having a particle size distribution with D_{90} < 250 μm. Reduction in particle size provides for greater surface area and hence better bioavailability. This also helps in uniform mixing of the drug with polymers and other excipients, which have a similar particle, size distribution.

The pH dependent hydrophilic polymers of the present invention may be selected from crosslinked acrylic acid based polymers and methacrylic acid polymers. The crosslinked acrylic acid polymers are carboxyvinyl polymers commercially available under the trade name "carbopol" from Noveon Inc. Company, Cleveland, Ohio, USA.

Carbopols preferred for use in the present invention include Carbopol 974P,Carbopol 971P and Carbopol 934P. Both Carbopol 974P and Carbopol 934P are highly crosslinked, have similar viscosity profile but the release pattern is different. Instead of the near zero order release profiles throughout the gastrointestinal tract observed in systems formulated with Carbopol 934P, Carbopol 974P provides a semi enteric release profile. Carbopol 971P is lightly cross-linked and provides a more linear and slow release.

Similarly, methacrylic acid copolymers commercially available as Eudragit ® by Rohm, Germany may be used. However use of Eudragit L and S is preferred.

The pH independent hydrophilic polymer of the present invention may be selected from cellulose ethers such as hydroxypropyl methylcellulose and hydroxypropyl cellulose commercially available from Dow Chemicals, USA and M/s Nisso, Japan under the trade names Methocel and HPC. Hydroxypropyl cellulose preferred for use in the present invention includes low viscosity grade polymer having molecular weight of about 80,000-1,00,000. Hydroxypropyl methylcellulose preferred for use in the present invention includes those having viscosity of 5-100cps.

The pH dependent hydrophilic polymers of the present invention control the sustained release characteristics of the nitrofurantoin.

Besides the above polymers sustained release portion may also contain other pharmaceutically acceptable excipients such as diluents, binders, stabilizers, antioxidants, preservatives, wetting agents, lubricants, glidants and colors.

Binders of the present invention may be selected from methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Diluents of the present invention may be selected from calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and mixtures thereof.

Lubricants and glidants of the present invention may be selected from colloidal anhydrous silica, stearic acid, sodium stearyl fumarate, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax and the like.

The colors of the present invention may be selected from any FDA approved colors for internal use.

The formulation of the present invention may optionally be coated, if desired.

The Immediate release portion of the dosage form may contain diluents, binders, disintegrants and lubricants besides nitrofurantoin as described above for sustained release portion.

The dosage form of the present invention may be in tablet or capsule form, however capsule form is preferred.

The immediate release portion is prepared by blending macrocrystalline nitrofurantoin with other pharmaceutically acceptable excipients and filing into the hard gelatin capsule. As immediate release portion provides immediate onset of action, the use of macrocrystalline nitrofurantoin is preferred due to lower incidence of nausea and emesis. To maintain the crystal structure of nitrofurantoin compression is normally avoided, as it may break the crystals and reduce the particle size. Therefore, immediate release portion is preferably filled in as such or in granular form.

The sustained release portion of the present dosage form is prepared by mixing micronized nitrofurantoin monohydrate with sustained release polymers and other pharmaceutically acceptable excipients. The blend can be filled as such, as granules or as loosely formed compact or tablet into a hard gelatin capsule.

The order in which the sustained release and immediate release mixtures are filled into the capsule shell is not important but preferably the two portions should form separate layers.

The invention is further illustrated by the following examples but it should not be construed as limiting the scope of the invention anyway.

Example 1

Immediate release portion	mg/cap
Nitrofurantoin Macrocrystals	25
Lactose	126.0
Starch	122.50
Magnesium stearate	1.50
Sustained Release portion	
Nitrofurantoin Monohydrate eq. to Nitrofurantoin	75.00
Carbopol® 971P	1.70
Carbopol® 974P	3.45
Hydroxypropylcellulose -L	2.50
Talc	2.20
Aerosil -200	1.10
Compressible Sugar	17.89
Magnesium stearate	1.0

Process

(Immediate Release)

- Drug, Lactose and Starch were sifted through suitable mesh and mixed.
- Magnesium Stearate was sifted through suitable mesh, and added to above blend and mixed well.
- The final blend was filled in hard gelatin capsule of appropriate size.

(Sustained release)

- All the ingredients were weighed.
- Drug and Aerosil were sifted together through suitable mesh followed by sifting of Carbopol 971P, 974P, Hydroxypropylcellulose-L, Sugar and Talc through suitable mesh. All ingredients were mixed thoroughly.
- The blend was compacted and then sized through suitable mesh.
- Lubricated with Magnesium Stearate and compressed.
- The resulting tablet was filled in hard gelatin capsule along with the immediate release portion.

Example-2

Immediate release portion	**mg/cap**
Nitrofurantoin Macrocrystals	25
Lactose	126.0
Starch	122.50
Magnesium stearate	1.50
Sustained Release portion	
Nitrofurantoin Monohydrate eq. to Nitrofurantoin	75.00
Carbopol® 934P	4.00
Hydroxypropyl Methyl Cellulose	8.00
Talc	1.0
Compressible Sugar	15.14
Sodium Stearyl Fumarate	1.70

Process

(Immediate Release)

- Drug, Lactose and Starch were sifted through suitable mesh and mixed.
- Magnesium Stearate was sifted through suitable mesh, and added to above blend and mixed well.
- The final blend was filled in hard gelatin capsule of appropriate size.

(Sustained release)

- All the ingredients were weighed.
- Drug, Carbopol® 934P, Hydroxypropylmethylcellulose, Sugar and Talc were sifted through suitable mesh. All ingredients were mixed thoroughly.
- The blend was compacted and then sized through suitable mesh.
- Lubricated with Sodium Stearyl Fumarate and compressed.
- The resulting tablet was filled in hard gelatin capsule along with immediate release portion.

Samples of the capsules prepared as per Example 1 and 2 were subjected to dissolution testing using USP apparatus 2, paddle speed 100 rpm, temperature 37°C, in simulated gastric fluid (0.01N HCl) for 1hour, followed by further 7 hours in phosphate buffer (pH 7.5). The samples taken from the dissolution medium at different time intervals were analyzed for nitrofurantoin. The rapid release and sustained release performance of the capsules of examples 1 &2 is shown in Table 1& 2 respectively.

Table 1: Dissolution of Nitrofurantoin capsules prepared as per the Example -1 in USP Apparatus-2 at 100rpm.

Time in hours	Cumulative % of Nitrofurantoin released	
	Dissolution media 0.01N HCl	Dissolution media pH 7.5 Phosphate buffer
1	11	
2		43
3		60
4		76
5		87
6		91
7		98
8		104

Table 2: Dissolution of Nitrofurantoin capsules prepared as per the Example -2 in USP Apparatus-2 at100rpm.

Time in hours	Cumulative % of nitrofurantoin released	
	Dissolution media 0.01N HCl	Dissolution media pH 7.5 Phosphate buffer
1	12	
2		48
3		60
4		70
5		76
6		80
7		90
8		98

WE CLAIM:

1. A process for the preparation of nitrofurantoin controlled release dosage form comprising:

a. A sustained release portion comprising

(i) Nitrofurantoin

(ii) One or more pH dependent hydrophilic polymer(s); and

b. An immediate release portion comprising macrocrystalline nitrofurantoin.

2. The process according to claim 1 wherein the sustained release portion further comprises of pH independent hydrophilic polymer.

3. The process according to claim 1 wherein the sustained release portion comprises of one pH dependent hydrophilic polymer.

4. The process according to claim 1 wherein the sustained release portion comprises of more than one pH dependent hydrophilic polymer.

5. The process according to claim 4 wherein the sustained release portion comprises of two pH dependent hydrophilic polymer.

6. The process according to claim 1 wherein pH dependent hydrophilic polymer is selected from the group consisting of cross-linked acrylic acid polymers or methacrylic acid derivatives.

7. The process according to claim 6 wherein cross-linked acrylic acid polymers are carboxyvinyl polymers.

8. The process according to claim 7 wherein carboxyvinyl polymer is carbopol® 974P.

9. The process according to claim 7 wherein carboxyvinyl polymer is Carbopol 971P.

10. The process according to claim 7 wherein carboxyvinyl polymer is carbopol® 934P.

11. The process according to claim 7 wherein carboxyvinyl polymer is combination of carbopol® 974P and Carbopol 971P.

12. The process according to claim 6 wherein methacrylic acid derivative is Eudragit® L.

13. The process according to claim 6 wherein methacrylic acid derivative is Eudragit® S.

14. The process according to claim 2 wherein pH independent hydrophilic polymer is cellulose ether.

15. The process according to claim 14 wherein cellulose ether is selected from hydroxypropyl methylcellulose and hydroxypropyl cellulose.

16. The process according to claim 15 wherein cellulose ether is Hydroxypropyl cellulose.

17. The process according to claim 16 wherein Hydroxypropyl cellulose is low viscosity grade polymer having molecular weight of about 80,000-1,00,000.

18. The process according to claim 15 wherein cellulose ether is Hydroxypropyl methylcellulose.

19. The process according to claim 1 wherein nitrofurantoin has a particle size distribution with D_{90}<250 μm.

20. The process according to claim 1 or 2 wherein sustained release portion additionally contains other pharmaceutically acceptable excipients.

21. The process according to claim 1 or 2 wherein the sustained release portion is in the form of powder, granules, compact or tablet.

22. The process according to claim 21 wherein the sustained release portion is in the form of tablet.

23. The process according to claim 1 wherein the immediate release portion is present in the form of powder or granule.

24. The process according to claim 23 wherein the immediate release portion is present in the form of powder.

25. The process according to claim 1 wherein dosage form is a capsule.

26. A process for the preparation of nitrofurantoin controlled release dosage form comprising sustained release and immediate release portions as described and exemplified herein.

Dated this **23rd** day of **August, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

PCT Application

IB0303517